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EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/260,624	Applicant(s) OHNISHI, TAKANORI	
	Examiner Mary Schmidt	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The request filed on August 1, 2001 (and completed on June 3, 2002), for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/260,624 is acceptable and a CPA has been established. An action on the CPA follows.

Claim Objections

2. The claims are objected to for minor formalities. Claims 1-6 specify the "RAD51" in capital letters whereas claims 9-14 specify the "Rad51" in lower case letters. Applicant is requested to choose one of the styles for uniformity.

3. Claims 17, 20, 23, 26 and 27 are objected to for grammatical inconsistency. Claims 17, 20, 23 and 26 specify that "said site is to a tumor" instead of just stating that the "site is a tumor". The site is the location of the administration of the antisense oligonucleotide, therefore, it "is" the site, and thus "is to a tumor" does not clearly define the site as the tumor. Furthermore, claim 27 would be more clearly stated if the site was claimed "as the tumor or where a tumor was previously located prior to removal" instead of making the "site" the object which "has a tumor or wherein a tumor has been removed."

Claim Rejections - 35 USC § 112

4.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-6 and 8-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to methods of inhibiting cell proliferation, inducing sensitivity to radiation or a chemotherapeutic agent, inhibiting the growth of a cancerous cell, and treating an individual via administration to said individual a Rad51 antisense molecule. The claims have a step of administration of the Rad51 antisense but do not have a final step relating back to the preamble so that the claimed function has been achieved.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6 and 8-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a method for inhibiting cell proliferation in an individual in vivo comprising administering to said individual a composition comprising a RAD51 antisense molecule. Claim 2 is drawn to a method for inducing sensitivity to radiation in an individual in vivo comprising administering to said individual a composition comprising a Rad51 antisense

molecule. Claim 3 is drawn to a method for inducing sensitivity to a chemotherapeutic agent in an individual in vivo comprising administering to said individual a composition comprising a RAD51 antisense molecule. Claim 4 is drawn to a method for inhibiting the growth of a cancerous cell comprising administering to said cell a composition comprising a Rad51 antisense molecule. Claim 5 is drawn to a method for inducing sensitivity to radiation in a cancerous cell comprising administering to said cell a composition comprising Rad51 antisense molecule. Claim 6 is drawn to a method for inducing sensitivity to a chemotherapeutic agent in a cancerous cell comprising administering to said cell a composition comprising Rad51 antisense molecule. Claim 8 specifies that the method of claim 1 further comprises the step of administering radiation. Claim 9 is drawn to a method of prolonging the survival of an individual comprising administration to said individual a Rad51 antisense molecule. Claim 11 is drawn to a method according to claim 10 wherein said administration comprises localized delivery of said Rad51 antisense molecule to a cancerous or potentially cancerous site. Claim 12 is drawn to a method according to claim 11 wherein said method further comprises radiation treatment at said site. Claim 13 is drawn to a method according to claim 11 wherein said method further comprises chemotherapeutic treatment of said patient. Claim 14 is drawn to a kit for diagnosing and/or treating cancer comprising a Rad51 antisense molecule. Claims 15-23 specify that the administration step the methods of claims 1, 18 and 21 is locally to a site wherein said cell proliferation is to be inhibited, wherein said administering is by injection, wherein said site is to a tumor. Claims 24-26 are drawn to the method of claim 9 wherein said individual is in need of

inhibition of cell proliferation, and wherein said administering is locally to a site wherein cell proliferation is to be inhibited, wherein said administration is by injection, to a tumor. Claims 27 and 28 further limit claim 11: wherein the site has a tumor or wherein a tumor has been removed, wherein said administering is by injection to a tumor.

The specification as filed taught the administration of Rad51 antisense (SEQ ID NOS: 1 and 2) which are the complement of both the human and mouse Rad51 gene (page 15 of the specification, "[t]he two 15-bp antisense oligonucleotides were complementary to a region showing homology between mouse and human sequences"), to mouse 203G glioma cells, and then *ex vivo* administration of said cells to mice in the cisterna magna via injection (page16 of the specification). The mice were further subjected to 6 Gy radiation and the specification taught on page 16 that "[t]he combination of Rad51 antisense oligonucleotides and 6 Gy irradiation extended the survival time much longer than did either treatment with radiation only or administration of the antisense alone... (Figure 5)." Applicant teaches on page 17 of the specification that "Anatomical and histological studies of dead mice revealed that a growing tumor mass occupied the basal cistern and cisterna magna and severely compressed the brain and spinal cord. In the dead mice treated with antisense oligonucleotide, fluorescence of FITC, which was labeled for the antisense oligonucleotides, was visualized in the tumor cells but a little in the normal tissues of brain and spinal cord."

Applicants work cited below (Ohnishi et al., Biochemical and Biophysical Research Communications 245, 319-324, 1998) clarifies (1) that the mouse 203G glioma cells were

administered to the mice prior to the antisense administration to the same site, and (2) that while the dead mice showed growth of gliomas, the mice that survived had not apparent tumors (page 323, col. A).

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> **The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.**

The claims as filed are drawn to administration of any Rad51 antisense to any species of whole organism. Note the specification as filed contemplates on page 8 that the "individual, or patient, is generally a human subject... the patient may be animal as well." However, since the

specification as filed only teaches two antisense to mouse/human Rad51 that function for antisense inhibition of the mouse Rad51 target gene *in vitro* and in mouse, one of skill in the art would not have recognized that Applicant was in possession of a representative number of species of any Rad51 to other animal species as broadly claimed. See the 35 U.S.C. 112, scope of enablement rejection below, for references citing the unpredictability in the antisense art for design of a functional antisense to a target gene for use in cells *in vivo*. Applicant has not provided in the specification as filed the necessary sequence structure of other antisense which bind to Rad51 from other species. One of skill in the art would not have been able to readily visualize the sequences of Rad51 antisense to other Rad 51 target genes from other organisms absent the specific sequence structure design criteria having the claimed antisense functions. (As noted in the rejection below, antisense technology is dependant on finding complementary antisense sequence which will bind with high affinity to a particular location of the target gene sequence so that the affinity is high enough to function for the desired *in vivo* functions.) It is the nature of the antisense art that the structure and function of one antisense does not provide guidance to the structure and function of other antisense. Each antisense must be evaluated on an antisense-by-antisense basis. The specification as filed provides adequate written description for administration of instant SEQ ID NO:1 and 2 to the specific regions of mice taught by way of example in the specification as filed. However, such description does not teach how to design either antisense to other species of Rad51, or how to design other Rad51 antisense for the claimed functions based on the instant disclosure. The description of the instant SEQ ID NOS: 1

and 2 in the specification does not supplement the omitted description of the specific sequence structure of other Rad51 antisense because specific, not general, guidance is what is needed. Furthermore, there is no evidence on the record of a relationship between the structure of the SEQ ID NOS:1 and 2 antisense and the structure of other antisense from humans or other animals that would provide any reliable information about the structure of other antisense having the claimed functions on the basis of the sequence of SEQ ID NOS: 1 and 2.

Applicant is thus not considered to have been in possession of antisense other than instant SEQ ID NOS: 1 and 2 for antisense inhibition of Rad51 in cells in cell culture and in specific target sites in mice since these two antisense do not constitute a "representative number of species" commensurate to the breath of any Rad51 antisense claimed (including the antisense in the kit of claim 14) and/or for the breath of *in vivo* functions claimed.

8. Claims 1-6 and 8-13 and 15-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delivery of Rad51 antisense of instant SEQ ID NO:1 and 2 to a mouse, does not reasonably provide enablement for any method of administration and treatment of any whole organism as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and practice the invention commensurate in scope with these claims for the same reasons of record as set forth in the Official actions mailed 11/08/99 and 08/01/00 (although the rejection is

newly stated and updated below). (Applicants have not provided any response to the Official Action mailed 08/01/00.)

See the description of the claims and the teachings of the specification and Applicants work (Ohnishi et al.) above.

The claims are drawn to methods treatment of a whole organism such as (1) inhibiting cell proliferation, (2) inducing sensitivity to radiation, (3) inducing sensitivity to a chemotherapeutic agent, (4) inhibiting growth of a cancerous cell, (5) prolonging the survival of an individual, and (6) treating cancer.

There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended

target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of

subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

The specification as filed teaches success of a locally administered, ie. injected, Rad51 antisense to a mouse, but such results are not predictive of (1) treatment effects via other routes of administration of said antisense, nor (2) correlation with whole organism success in other organisms such as human.

In regards to point (1) above, routes of administration of the antisense *in vivo*, the teaching of direct injection of an antisense does not correlate to other routes of administration to cells *in vivo*. As argued above, the antisense must be able to efficiently target the desired target gene location. Fritz et al. and Chirila et al. Teach common concerns in the design of suitable delivery vehicles for antisense oligonucleotides but teach the necessarily factors to be considered in the process. For instance Fritz et al. teach on page 272 that "[a]n efficient and versatile drug carrier system has to fulfill the following requirements: (I) particle sizes in the submicrometer range; (ii) the possibility of surface modification; (iii) high drug loading capacity; (iv) colloidal stability of the latex in biological media; and (v) the lack of toxic side effects induced by the carrier or additives." Chirila et al. teach on mechanism of antisense action in vivo and the necessary requirement that the antisense be able to internalize into the desired cell target (see page 325). They teach on page 327 that "[e]ncapsulation or incorporation in liposomes is currently the preferred method for the delivery of AS ODNs... and, besides the intravenous infusion and subcutaneous, intramuscular or intraocular injection of naked ODNs, probably the only other method used in human clinical trials. (Ultimately, the suspensions of liposomes are also administered by infusion or injection.)." They also teach that the "in vivo delivery techniques chiefly used at the present, i.e. infusion or injection of naked molecules and liposomal systems, do not assure adequately long-term maintenance of ODNs in tissues." Without further guidance in the specification as filed for mechanisms for administration of the disclosed Rad51 antisense to other cancerous tissues in the desired subject, one skilled in the art would necessary

practice "trial and error" experimentation to design and implement successful regimens for administration of the Rad51 antisense for the claimed functions. For instance, there is no guidance in the specification as filed as to how to avoid almost certain toxicity of administration of antisense to Rad51 (a gene expressed in many tissues in vivo) systemically.

In regards to point (2) above, correlation of murine and human treatment data, note Crystal who teaches the unpredictability in the art of correlated success between administration of therapeutic nucleic acid constructs to mice and humans (see especially page 40, col. A). Neither the specification nor the prior art taught how the *ex vivo* administration of tumor cells to mice, followed by antisense administration correlates to the actual administration of said antisense to other types of cancerous cells in other whole organisms. Resor et al. taught a review on mouse modeling techniques useful for modeling human cancer. They teach in the specification that "transgenic approaches do no always completely and accurately model human carcinogenesis." They teach on page 669 that "[a]lthough these techniques have provided great insight, they do not fully model the vast majority of cases of cancer. In general, cancer arises because individual somatic cells sustain a series of sequential mutations that provide a growth or survival advantage, escape from senescence and the onset of genomic instability, thus perpetuating genetic changes that ultimately result in tumor formation. Standard transgenic and knockout techniques do not faithfully model such changes." The instant claims are drawn to inhibiting any cell proliferation in any individual *in vivo* comprising the administering to said individual a composition comprising a Rad51 antisense. The teachings of *ex vivo* administration

of one type of cancer cell to mice followed by antisense delivery to the site, does not correlate to any other treatment effects of any cancer as broadly claimed in any whole organism. The teachings of Resor et al. summarize the lack of uniformity among the causes of different types of cancer, which preclude equivalent treatment of any such cancer in any individual. For another specific example of the lack of correlation between murine and human cancer pathology, Applicant is referred to the teachings of Blackshear. She taught on pages 105-106 that "[a]nimal models of spontaneous and chemically induced mammary gland carcinogenesis have provided some insight into the pathogenesis of breast cancer but do not faithfully mimic the pathology or biological behavior of human breast cancer.... there is no single model that best mimics the pathology and mechanistic deregulation seen in breast cancer. Each model provides a small portion of the puzzle, which helps to clarify the complex interactions associated with eh heterogeneous population of cells in the normal mammary gland. These models enable the researcher to examine individual or combinations of perturbations that lead to the initiation and progression of breast cancer." Thus, absent use of an art recognized mouse model of human disease, the art teaches a high level of unpredictability for the correlation of specific treatment results in mice with an expectation of success of the equivalent effects in humans.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* organisms other than mouse for the breadth of functions claimed in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment

effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. The quantity of experimentation would require the *de novo* determination of the unpredictable factors argued above for the breadth of treatments encompassed by the instant claims. Therefore, it would require undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claim 14 is rejected under 35 U.S.C. 102(b) as being anticipated by Taki et al. (Biochem. Biophys. Res. Commun. 223:434-438, 1996, cited in the Official Action mailed 11/8/99).

Claim 14 is drawn to a kit for diagnosing and/or treating cancer comprising a Rad51 antisense molecule. The functional language "diagnosing and/or treating cancer" is not considered to breath further life and meaning into what was an already known composition, a Rad51 antisense. Taki et al. taught the two antisense oligonucleotide sequences of instant SEQ ID NOS. 1 and 2 (page 434) which bind to Rad51. Since a kit is a composition claim, and the composition is the Rad51 antisense, Taki et al. anticipated instant claim 14.

11. Claims 1, 2, 4, 5, 8-12 and 14-28 are rejected under 35 U.S.C. 102(a) as being anticipated by Ohnishi et al. (Biochem. Biophys. Res. Comm. 245:319-324, 1998).

Ohnishi et al. taught the same experiments disclosed in the instant specification (Applicant's own work). They taught administration of instant SEQ ID NOS:1 and 2 to the mouse 203G cells *in vivo* coupled with radiation treatment. They show that the administration of the Rad51 antisense was able to inhibit cell proliferation in the mouse, induce sensitivity to radiation in the mouse, and reduce the cancerous growth of the 203G cells *ex vivo*. They taught direct injection of the antisense oligonucleotides (see pages 320 and 323 especially). Since they taught the sequences of instant SEQ ID NOS:1 and 2 they further anticipated claim 14 drawn to a kit for diagnosing and/or treating cancer comprising a Rad51 antisense molecule. The functional language "diagnosing and/or treating cancer" is not considered to breath further life and meaning into what was an already known composition, a Rad51 antisense. Since a kit is a composition claim, and the composition is the Rad51 antisense, Ohnishi et al. anticipated instant claim 14.

12. Claims 3, 6 and 13 are free of the prior art since neither Taki et al. nor Ohnishi et al. taught nor fairly suggested the administration of Rad51 antisense with chemotherapeutic treatment for inducing sensitivity to a chemotherapeutic agent and/or treatment of cancer for the enabled breath of the instant claims for treatment in mice. Although chemotherapeutic agents were known in the prior art, there was no motivation or suggestion to combine administration of any known chemotherapeutic agent with Rad51 antisense oligonucleotide for inducing sensitivity to a chemotherapeutic agent and/or treatment of cancer. There was not an expectation of success taught in the prior art that co-administration of Rad51 antisense to an individual coupled with chemotherapy would function as a method of treating cancer and/or inducing sensitivity to a chemotherapeutic agent.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Kay Pinkney*, whose telephone number is (703) 305-3553.

M. M. Schmidt
August 25, 2002